Atrial Fibrillation Treatment 2011

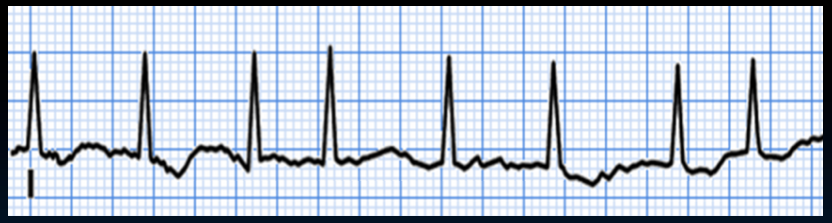
John Mandrola

Disclosures

None

Approach to AF treatment

(after making the diagnosis and exclusion of obvious causes)



Treat Symptoms

Rhythm Control

Prevent Heart Failure

Rate Control

Prevent Stroke

Anticoagulants

Devices

Ablation

Topics for today

An AF doctor's approach to preventing stroke

What's the best tool for treating AF?

- Drugs?
- Devices?
- Ablation?

Education
Knowledge

Education
6 Things that I explain

- What is AF?
- What causes AF?
- What our the goals of treatment?
  - Cures are rare
- What are the possible treatments?
- The importance of treating associated conditions
  - TLC – *Therapeutic Lifestyle Changes*
- The Quandary…

The Quandary

AF AF RX

AF Treatment…Bad?

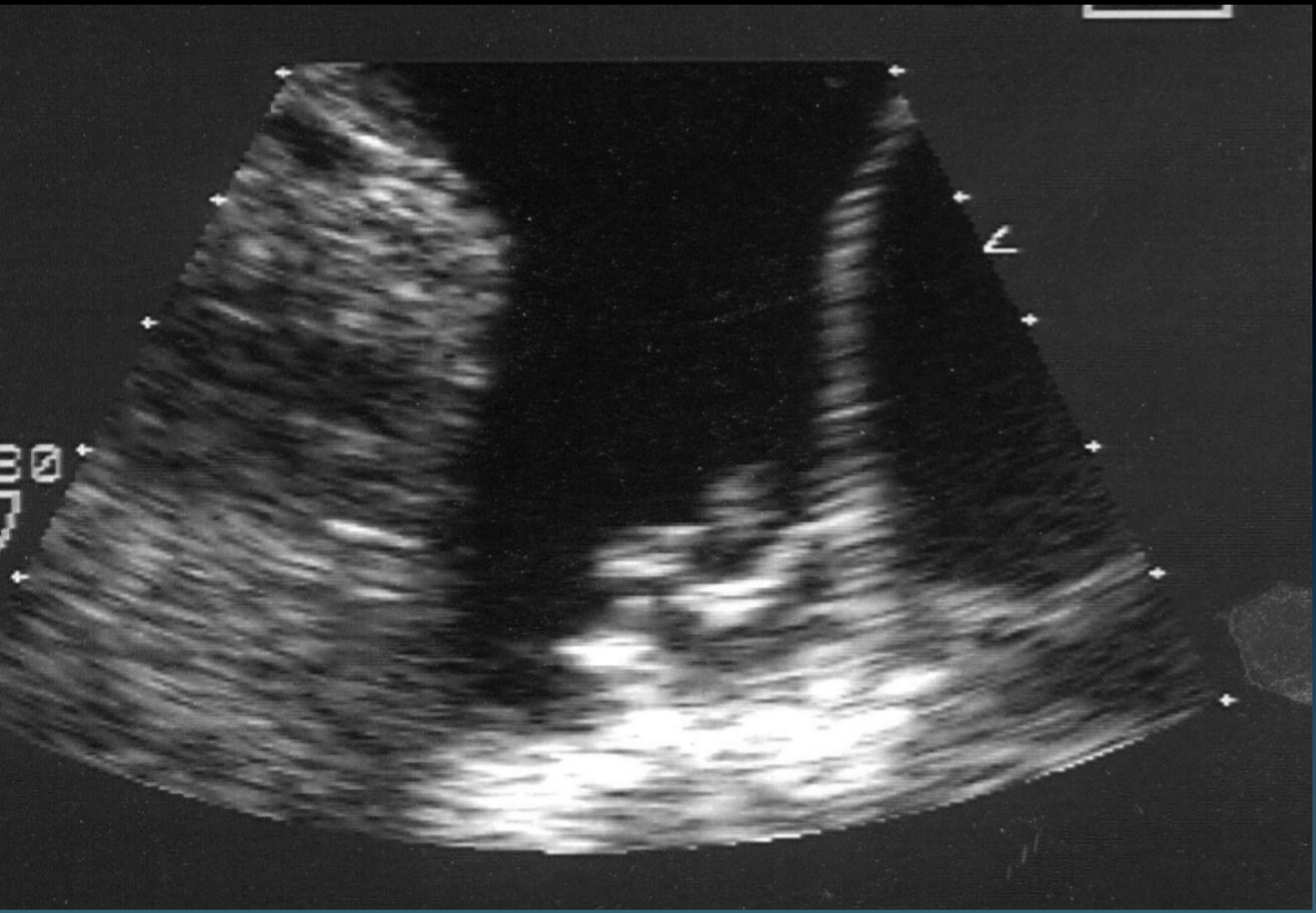
- **Prolonged QT and VF**
  - Sotalol, Dofetilide, Amiodarone, dronedarone
- **1:1 Atrial Flutter and syncope and SCD**
  - Propafenone, Flecanide
- **Organ toxicity (Liver, Lung and Thyroid)**
  - Amio, Dronedarone
- Bleeding from blood thinners
- **Severe Bradycardia warranting an implantable intravascular device**
  - All AF drugs except dofetilide
- **Fatigue, exercise Intolerance and shortness of breath**
  - All AF drugs except dofetilide
- **Complications from catheter ablation**
  - Death, Stroke, Pericardial tamponade, Phrenic nerve paralysis, PV stenosis, Pulmonary emboli, pneumonia, vascular complications

Humbling

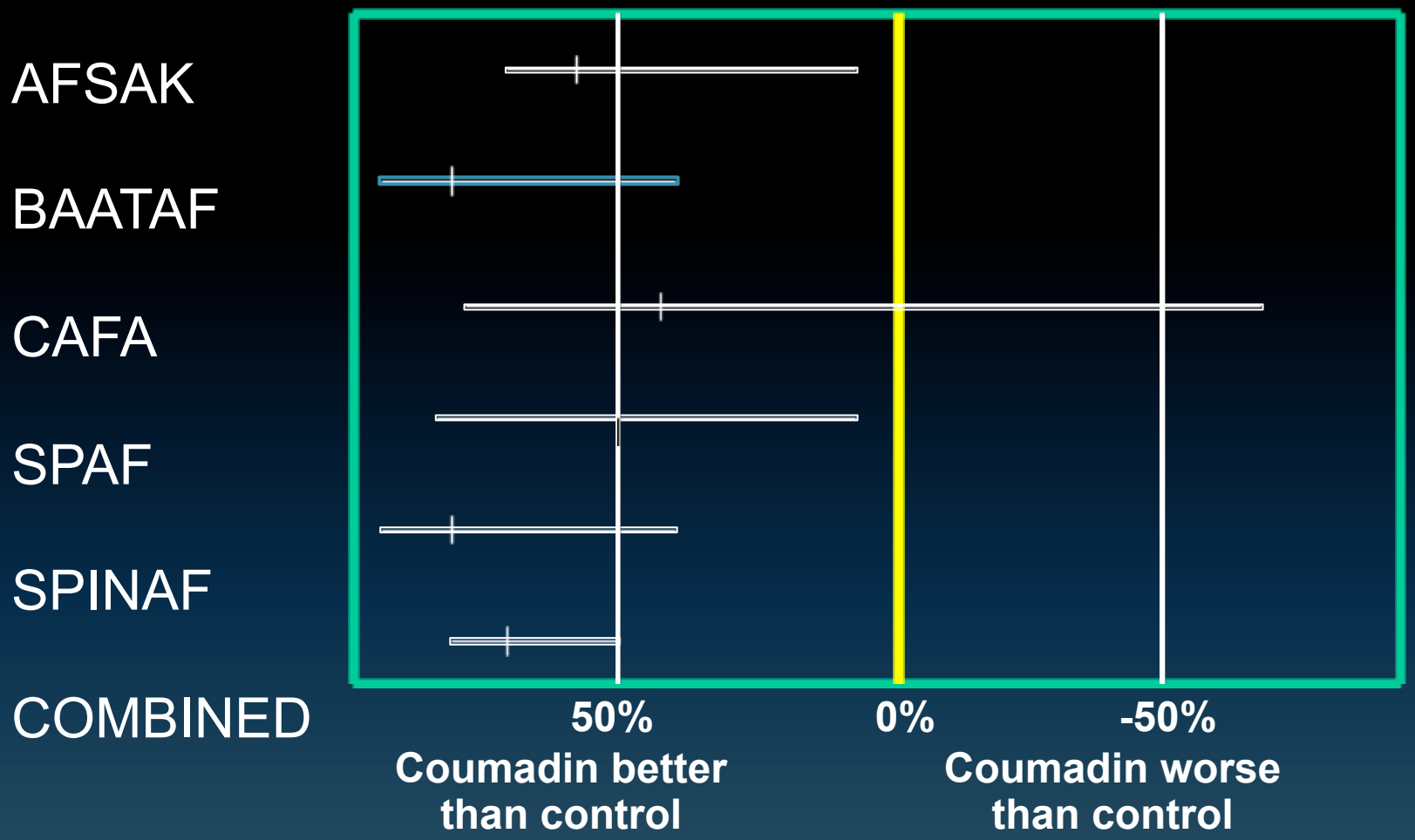
Stroke in AF
Possible reasons

- Loss of mechanical systole
- Stasis of blood
- Atrial fibrosis
- Platelet activation
- (E) All of the above

Left Atrial Appendage clot in AF



Plot of 5 Randomized trials of Thrombo-embolic Prevention with Warfarin



Stroke in AF
Myths

1. **Rhythm-control strategies** prevent stroke
2. **Running the INR on the low side** (< 2) is an effective strategy for lowering risk of bleeding and still getting some stroke prevention
3. Intermittent AF confers less stroke risk than permanent AF
4. **Aspirin** offers the elderly AF patient a safer and effective strategy of stroke prevention

    -BAFTA

    -AVEROS

    -Danish Registry study (10-11)

Does rhythm control prevent stroke?

AFFIRM lessons

Event	Overall (N=4060)	Rate-Control Group (N=2027)	Rhythm-Control Group (N=2033)	P Value
		no. of patients (%)		
Primary end point (death)	666 (26.3)	310 (25.9)	356 (26.7)	0.08†
Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)	861 (32.3)	416 (32.7)	445 (32.0)	0.33
Torsade de pointes	14 (0.5)	2 (0.2)‡	12 (0.8)	0.007
Sustained ventricular tachycardia	15 (0.6)	9 (0.7)	6 (0.6)	0.44
Cardiac arrest followed by resuscitation				
Ventricular fibrillation or ventricular tachycardia	19 (0.6)	10 (0.7)	9 (0.5)	0.83
Pulseless electrical activity, bradycardia, or other rhythm	10 (0.3)	1 (<0.1)	9 (0.6)	0.01
Central nervous system event				
Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
After discontinuation of warfarin	69	25	44	
During warfarin but with INR <2.0	44	27	17	
Concurrent atrial fibrillation	67	42	25	
Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68

AFFIRM Trial NEJM 2002

Stroke in AF
Myths

1. **Rhythm-control strategies** prevent stroke
2. **Running the INR on the low side** (< 2) is an effective strategy for lowering risk of bleeding and still getting some stroke prevention
3. Intermittent AF confers less stroke risk than permanent AF
4. **Aspirin** offers the elderly AF patient a safer and effective strategy of stroke prevention

    -BAFTA

    -AVEROS

    -Danish Registry study (10-11)

Ischemic Stroke and ICH in AF

Table 5. Incidence Rates of Ischemic Stroke and Intracranial Hemorrhage among Patients with Nonvalvular Atrial Fibrillation Who Were Taking Warfarin, According to the International Normalized Ratio (INR) at the Time of the Stroke.*

INR	Person-yr†	Stroke (95% CI) (N=152)	Person-yr†	Intracranial Hemorrhage (95% CI) (N=58)
		rate/100 person-yr		*rate/100 person-yr*
<1.5	556	7.7 (5.7–10.4)	561	0.5 (0.2–1.7)
1.5–1.9	2847	1.9 (1.4–2.4)	2867	0.3 (0.1–0.6)
2.0–2.5	5357	0.4 (0.3–0.7)	5400	0.3 (0.2–0.4)
2.6–3.0	2388	0.9 (0.6–1.4)	2409	0.5 (0.3–0.9)
3.1–3.5	834	0.7 (0.3–1.6)	843	0.6 (0.3–1.4)
3.6–3.9	243	0.4 (0.1–2.9)	247	0.4 (0.1–2.9)
4.0–4.5	144	1.4 (0.4–5.5)	147	2.7 (1.0–7.3)
>4.5	115	2.6 (0.8–8.1)	118	9.4 (5.2–16.9)

* CI denotes confidence interval.
† Differences in the numbers of person-years between stroke and intracranial hemorrhage reflect differences in the time at which data were censored.

- 13K patients with AF and stroke
  - Kaiser Permanente Northern CA
- SubRx INR assoc with Inc stroke severity, inc mortality and no fewer ICH

Threshold of Increased ICH

Hylek EM et al. N Engl J Med 2003;349:1019-1026.

The NEW ENGLAND JOURNAL of MEDICINE

Severity of stroke, according to the intensity of blood-thinner

Table 2. Severity of the Neurologic Deficit at Discharge and 30-Day Mortality Rates, According to the Antithrombotic-Medication Status and International Normalized Ratio (INR) at Admission.

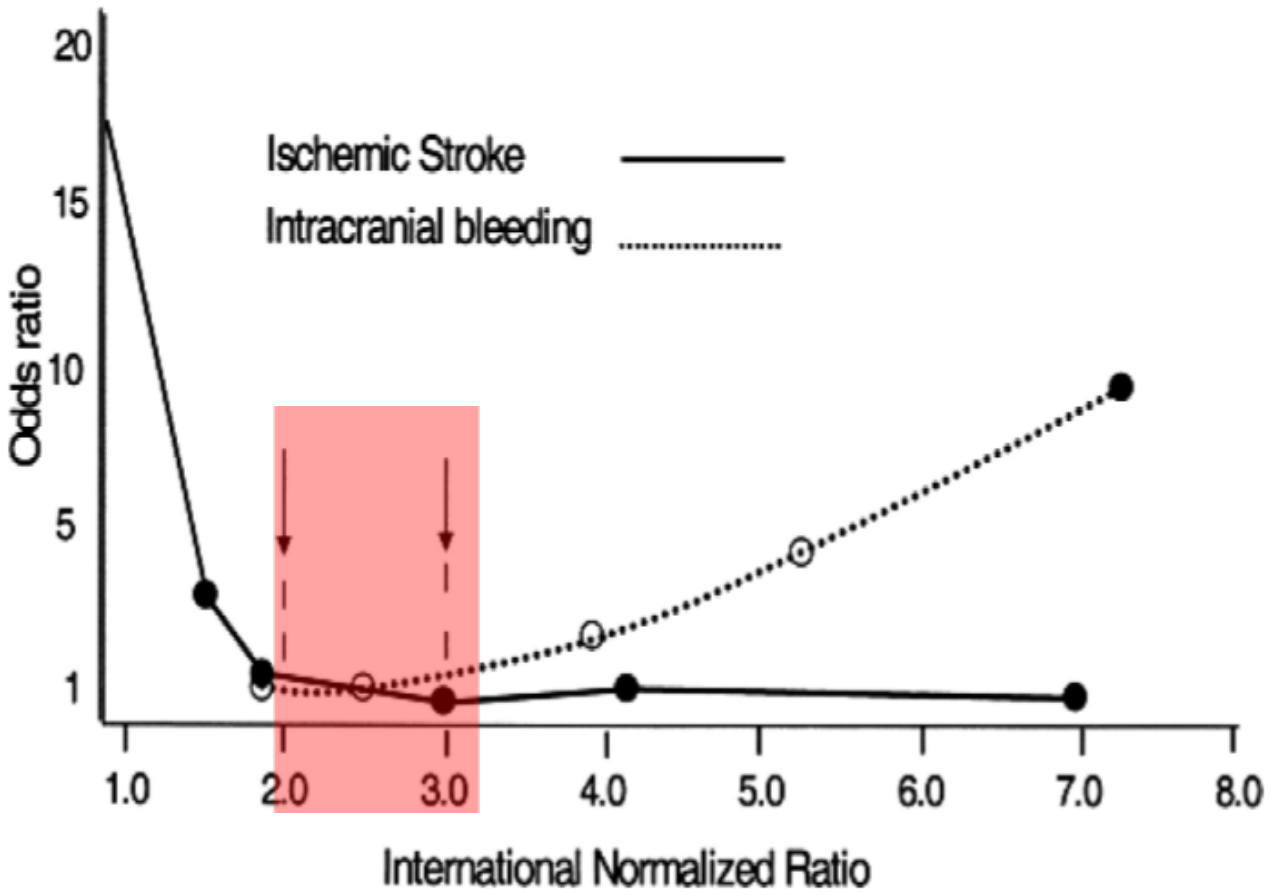
Variable	None (N=248)	Aspirin (N=160)	Warfarin	
			INR <2.0 (N=117)	INR ≥2.0 (N=71)
	percent			
Severity and outcome of stroke				
Fatal in-hospital stroke	14	6	9	1
Severe stroke, total dependence	8	7	6	4
Major stroke, neurologic deficit that prevented independent living	37	36	44	38
Minor stroke, neurologic deficit that did not prevent independent living	36	49	38	55
No neurologic sequelae	5	2	3	2
Total 30-day mortality	24	15	16	6

Adequate blood-thinning assoc with less severe neurologic events

Hylek EM et al. N Engl J Med 2003;349:1019-1026.

The NEW ENGLAND JOURNAL of MEDICINE

Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to inter of anticoagulation



Fuster, V. et al. J Am Coll Cardiol 2006;48:e149–e246

JACC Journal of the American College of Cardiology

Stroke in AF
Myths

1. **Rhythm-control strategies** prevent stroke
2. **Running the INR on the low side** (< 2) is an effective strategy for lowering risk of bleeding and still getting some stroke prevention
3. Intermittent AF confers less stroke risk than permanent AF
4. **Aspirin** offers the elderly AF patient a safer and effective strategy of stroke prevention

    -BAFTA

    -AVEROS

    -Danish Registry study (10-11)

Stroke Risk: Intermittent AF versus Persistent/Permanent

European Guidelines

- *Patients with paroxysmal AF should be regarded as having a stroke risk similar to those with persistent or permanent AF, in the presence of risk factors.*

Stroke in AF
Myths

1. **Rhythm-control strategies** prevent stroke
2. **Running the INR on the low side** (< 2) is an effective strategy for lowering risk of bleeding and still getting some stroke prevention
3. Intermittent AF confers less stroke risk than permanent AF
4. **Aspirin** offers the (elderly) AF patient a safer and equally effective strategy for preventing stroke

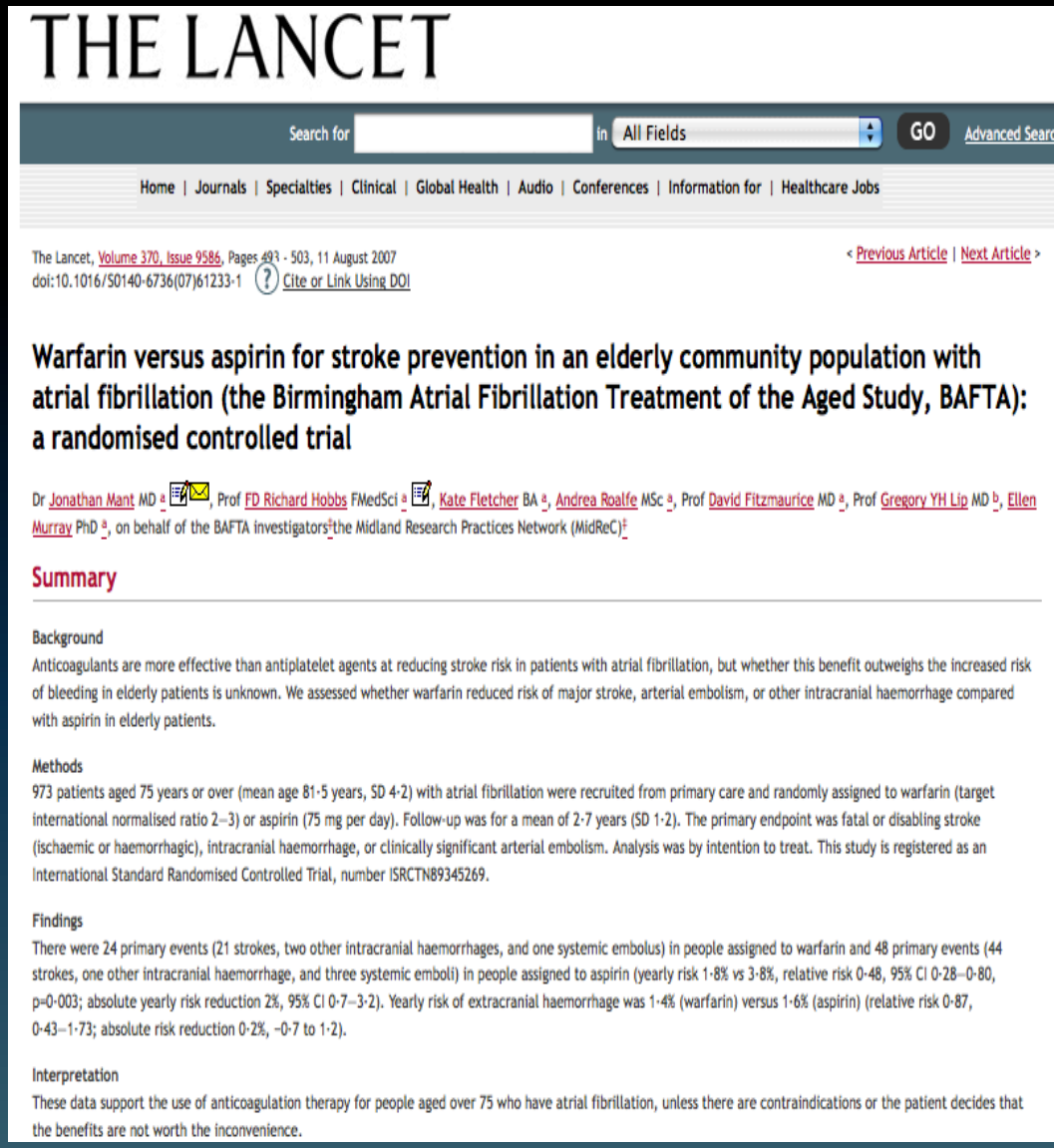
    -BAFTA

    -AVEROS

    -Danish Registry study (October 2011)

BAFTA Trial (2007)

- Real-world cohort of 975 elderly patients (>75 years) w/AF (Private practice)
- OAC vs ASA
- Far fewer strokes with OAC (RR =52%)
- *No differences in ICH or bleeding*



THE LANCET

Search for in All Fields GO Advanced Search

Home | Journals | Specialties | Clinical | Global Health | Audio | Conferences | Information for | Healthcare Jobs

The Lancet, Volume 370, Issue 9586, Pages 493 - 503, 11 August 2007
doi:10.1016/S0140-6736(07)61233-1 Cite or Link Using DOI

< Previous Article | Next Article >

Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

Dr Jonathan Mant MD [a], Prof FD Richard Hobbs FMedSci [a], Kate Fletcher BA [a], Andrea Roalfe MSc [a], Prof David Fitzmaurice MD [a], Prof Gregory YH Lip MD [b], Ellen Murray PhD [a], on behalf of the BAFTA investigators[‡]the Midland Research Practices Network (MidReC)[‡]

Summary

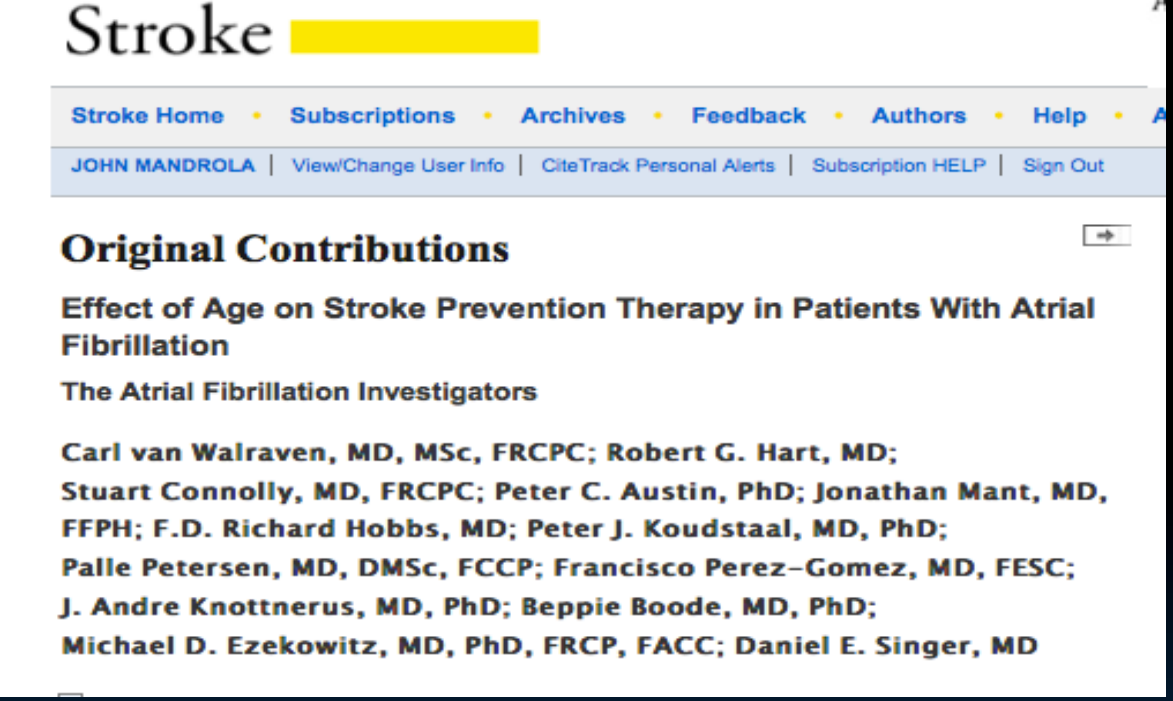
Background
Anticoagulants are more effective than antiplatelet agents at reducing stroke risk in patients with atrial fibrillation, but whether this benefit outweighs the increased risk of bleeding in elderly patients is unknown. We assessed whether warfarin reduced risk of major stroke, arterial embolism, or other intracranial haemorrhage compared with aspirin in elderly patients.

Methods
973 patients aged 75 years or over (mean age 81·5 years, SD 4·2) with atrial fibrillation were recruited from primary care and randomly assigned to warfarin (target international normalised ratio 2–3) or aspirin (75 mg per day). Follow-up was for a mean of 2·7 years (SD 1·2). The primary endpoint was fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN89345269.

Findings
There were 24 primary events (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in people assigned to warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin (yearly risk 1·8% *vs* 3·8%, relative risk 0·48, 95% CI 0·28–0·80, p=0·003; absolute yearly risk reduction 2%, 95% CI 0·7–3·2). Yearly risk of extracranial haemorrhage was 1·4% (warfarin) versus 1·6% (aspirin) (relative risk 0·87, 0·43–1·73; absolute risk reduction 0·2%, −0·7 to 1·2).

Interpretation
These data support the use of anticoagulation therapy for people aged over 75 who have atrial fibrillation, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience.

Effect of Age on Stroke Prevention RX in AF (2009-Stroke)



Stroke

Stroke Home • Subscriptions • Archives • Feedback • Authors • Help •

JOHN MANDROLA | View/Change User Info | CiteTrack Personal Alerts | Subscription HELP | Sign Out

Original Contributions

Effect of Age on Stroke Prevention Therapy in Patients With Atrial Fibrillation

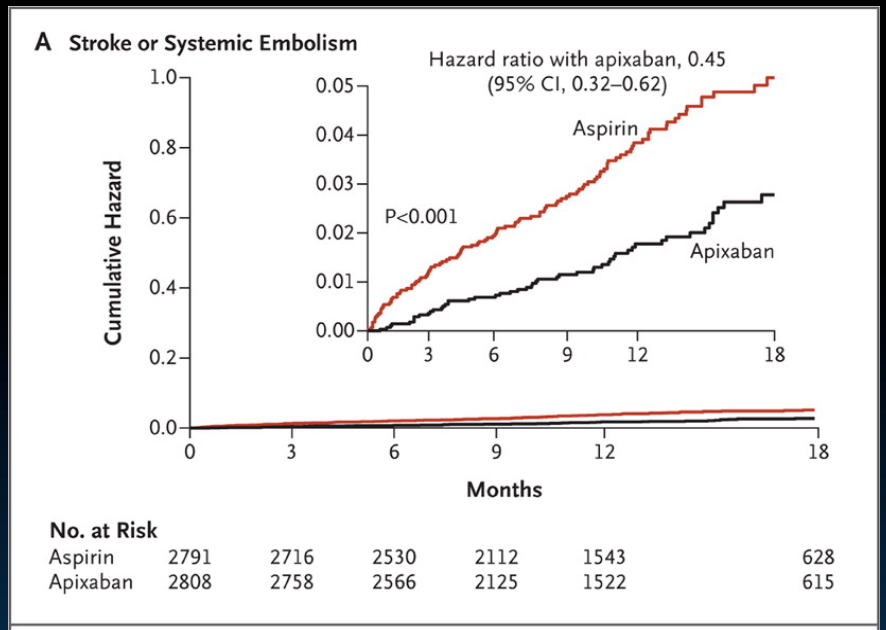
The Atrial Fibrillation Investigators

Carl van Walraven, MD, MSc, FRCPC; Robert G. Hart, MD; Stuart Connolly, MD, FRCPC; Peter C. Austin, PhD; Jonathan Mant, MD, FFPH; F.D. Richard Hobbs, MD; Peter J. Koudstaal, MD, PhD; Palle Petersen, MD, DMSc, FCCP; Francisco Perez–Gomez, MD, FESC; J. Andre Knottnerus, MD, PhD; Beppie Boode, MD, PhD; Michael D. Ezekowitz, MD, PhD, FRCP, FACC; Daniel E. Singer, MD

- Meta-Analysis of 8000+ patients from RCT of OAC and ASA
- Results:
  - Relative benefit of OAC did not vary by age
  - Increased bleeding risk with OAC was far smaller than beneficial reduction in stroke
  - Relative benefit of ASA decreased with increasing age.
- Conclusion:

Because stroke risk increases with age, the absolute benefit of OAC increases as patients age

AVEROS Trial (NEJM 2010)



- 5000+ warfarin-unsuitable AF patients randomized to Apixaban or ASA
- Apixaban sig reduced risk of stroke without an increase in bleeding

Connolly SJ et al. N Engl J Med 2011;364:806-817.

The NEW ENGLAND JOURNAL of MEDICINE

Thromb Haemost. 2011 Sep 27;106(4):739-49. Epub 2011 Jul 20.

Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study.

Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C.

Jonas Bjerring Olesen, Department of Cardiology, Post 635, Copenhagen University Hospital Gentofte, Niels Andersens Vej 65, 2900 Hellerup, Denmark, Tel.: +45 2361 7139, Fax: +45 7020 1283, E-mail: jo@heart.dk.

Abstract

It was the aim of this study to determine the efficacy and safety of vitamin K antagonists (VKAs) and acetylsalicylic acid (ASA) in patients with non-valvular atrial fibrillation (AF), with separate analyses according to predicted thromboembolic and bleeding risk. By individual level-linkage of nationwide registries, we identified all patients discharged with non-valvular AF in Denmark (n=132,372). For every patient, the risk of stroke and bleeding was calculated by CHADS2, CHA2DS2-VASc, and HAS-BLED. During follow-up, treatment with VKA and ASA was determined time-dependently. VKA consistently lowered the risk of thromboembolism compared to ASA and no treatment; the combination of VKA+ASA did not yield any additional benefit. In patients at high thromboembolic risk, hazard ratios (95% confidence interval) for thromboembolism were: 1.81 (1.73-1.90), 1.14 (1.06-1.23), and 1.86 (1.78-1.95) for ASA, VKA+ASA, and no treatment, respectively, compared to VKA. The risk of bleeding was increased with VKA, ASA, and VKA+ASA compared to no treatment, the hazard ratios were: 1.0 (VKA; reference), 0.93 (ASA; 0.89-0.97), 1.64 (VKA+ASA; 1.55-1.74), and 0.84 (no treatment; 0.81-0.88), respectively. There was a neutral or positive net clinical benefit (ischaemic stroke vs. intracranial haemorrhage) with VKA alone in patients with a CHADS2 score of ≥ 0, and CHA2DS2-VASc score of ≥ 1. This large cohort study confirms the efficacy of VKA and no effect of ASA treatment on the risk of stroke/thromboembolism. Also, the risk of bleeding was increased with both VKA and ASA treatment, but the net clinical benefit was clearly positive, in favour of VKA in patients with increased risk of stroke/thromboembolism.

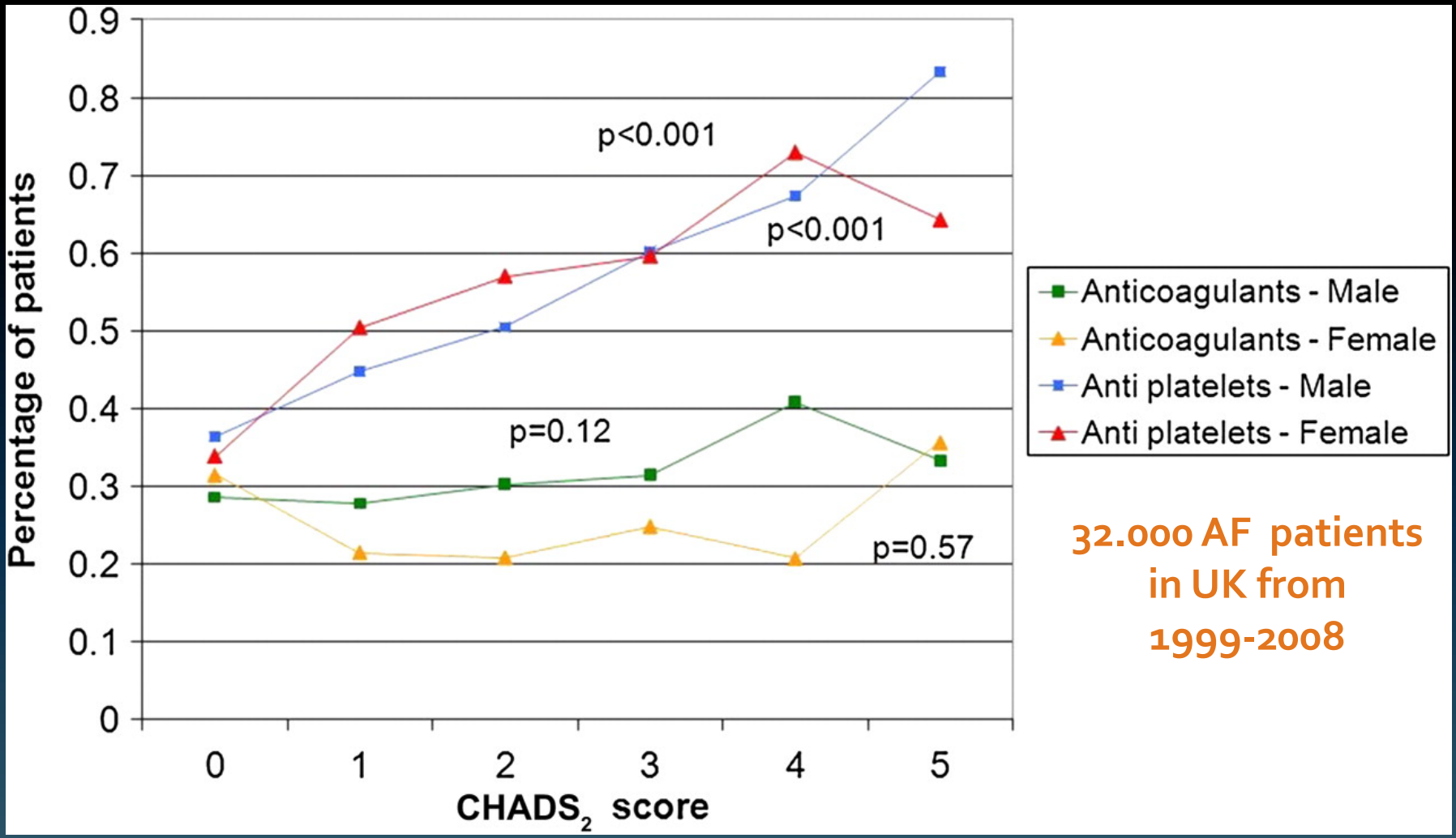
Risks of stroke and bleeding in patients with AF: A net clinical benefit analysis using a 'real world' nationwide cohort study. (2011)

- 132,000 Danish AF patients
  - F/U 7 days to 12 years
- Warfarin alone consistently decreased stroke risk
  - Except in very low risk patients (CHADS2 = 0)
- ASA ineffective compared to OAC
- Bleeding Risk increased with ASA, Warfarin, Combination
  - Highest bleeding risk w/combination

Despite all the data…

- ASA is still overused;
- Anticoagulants underused;
- Patients at highest risk not being anti-coagulated;
- Females less aggressively treated

Percentage of AF patients treated with anticoagulant and antiplatelet therapy prior to stroke by CHADS2 score.



32.000 AF patients in UK from 1999-2008

Lee S et al. BMJ Open 2011;1:e000269

Deciding on anticoagulation…

Stratification of stroke risk in AF

CHADS2

	Points
• Congestive Failure	1
– (LV dysfunction)	
• HTN	1
• Age > 75	1
• Diabetes	1
• Stroke (previous stroke /TIA)	2

JAMA 2001

$CHADS_2$ score and stroke rate

$CHADS_2$ score	Patients (n = 1733)	Adjuste stroke rate (%/y)* (95% confidence interval)
0	120	1.9 (1.2 - 3.0)
1	463	2.8 (2.0 - 3.8)
2	523	4.0 (3.1 - 5.1)
3	337	5.9 (4.6 - 7.3)
4	220	8.5 (6.3 - 11.1)
5	65	12.5 (8.2 - 17.5)
6	5	18.2 (10.5 - 27.4)

Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of AF JAMA 2001;285:2864 – 2870.

North American (AHA/ACC/HRS) guidelines for stroke prevention

- CHADS2 = 0 → Nothing or ASA
- CHADS2 = 1 → Anticoag or ASA
- CHADS2 >= 2 → Anticoag (INR 2-3)

Advantages of CHADS2

- Simple (That's always good.)
- Concrete
- Easy to remember
- Validated with a good evidence base

Weakness of CHADS2 Is it too simple?

- How low risk is Zero?
- Intermediate Risk is broad:
  - CHADS2 =1 represents a diverse and large cohort
  - Given the North American guidelines for CHADS =1 ASA or Anticoag, CHADS2 leaves the door open for under-treatment with ASA

CHADS2 Cases

- CHADS2 = 0 :
  - 74 year-old female smoker with severe CAD
  - 34 year old medical student
- CHADS2 = 1:
  - 74 year-old female with severe CAD and diabetes
  - 34 year-old medical student w/HTN

Can we do better than CHADS2?

CHA_2DS_2-VASc

- + Female Gender
- + Age 65-74
- + Vascular disease
  - CAD
  - PAD
  - Aortic Plaque

Table 8 CHA_2DS_2VASc score and stroke rate

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]
(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc

(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

$CHADS_2$ -> CHA_2DS_2VASc

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

From ESC AF Guidelines

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

$CHADS_2$ -> CHA_2DS_2VASc

CHADS2 score	Patients (*n* = 1733)	Adjusted stroke rate %/ year
0	120	1.9
1	463	2.8
2	523	4.0
3	337	5.9
4	220	8.5
5	65	12.5
6	5	18.2

CHA2DS2-VASc score	Patients (*n* = 7329)	Adjusted stroke rate (%/ year)
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

From ESC AF Guidelines: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

Table 2

Event rate (95% CI) of hospital admission and death due to thromboembolism* per 100 person years

Score/risk category	1 year's follow-up	5 years' follow-up	10 years' follow-up
$CHADS_2$:			
0	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
1	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
2	7.34 (6.88 to 7.82)	5.58 (5.35 to 5.83)	5.40 (5.18 to 5.63)
3	15.47 (14.62 to 16.36)	10.29 (9.87 to 10.73)	9.89 (9.50 to 10.31)
4	21.55 (20.03 to 23.18)	14.00 (13.22 to 14.82)	13.70 (12.95 to 14.48)
5	19.71 (16.93 to 22.93)	12.98 (11.52 to 14.63)	12.57 (11.18 to 14.14)
6	22.36 (14.58 to 34.30)	16.75 (11.91 to 23.56)	17.17 (12.33 to 23.92)
$CHADS_2$:			
Low risk (0)	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
Intermediate risk (1)	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
High risk (2-6)	12.27 (11.84 to 12.71)	8.30 (8.08 to 8.51)	7.97 (7.77 to 8.17)
CHA_2DS_2-VASc:			
0	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
1	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
2	3.71 (3.36 to 4.09)	3.01 (2.83 to 3.20)	2.92 (2.76 to 3.09)
3	5.92 (5.53 to 6.34)	4.41 (4.21 to 4.61)	4.28 (4.10 to 4.47)
4	9.27 (8.71 to 9.86)	6.69 (6.41 to 6.99)	6.46 (6.20 to 6.74)
5	15.26 (14.35 to 16.24)	10.42 (9.95 to 10.91)	9.97 (9.53 to 10.43)
6	19.74 (18.21 to 21.41)	12.85 (12.07 to 13.69)	12.52 (11.78 to 13.31)
7	21.50 (18.75 to 24.64)	13.92 (12.49 to 15.51)	13.96 (12.57 to 15.51)
8	22.38 (16.29 to 30.76)	14.07 (10.80 to 18.33)	14.10 (10.90 to 18.23)
9	23.64 (10.62 to 52.61)	16.08 (8.04 to 32.15)	15.89 (7.95 to 31.78)
CHA_2DS_2-VASc:			
Low risk (0)	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
Intermediate risk (1)	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
High risk (2-9)	8.82 (8.55 to 9.09)	6.01 (5.88 to 6.14)	5.72 (5.60 to 5.84)

*Includes peripheral artery embolism, ischaemic stroke, and pulmonary embolism.

$CHADS_2$ vs CHA_2DS_2-VASc

- 73,000 AF patients in Denmark registry, not treated with warfarin and followed clinically from 1997-29006
- How did the two validation schemes compare?

BMJ 2011; 342:d124

Table 2

Event rate (95% CI) of hospital admission and death due to thromboembolism* per 100 person years

Score/risk category	1 year's follow-up	5 years' follow-up	10 years' follow-up
$CHADS_2$:			
0	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
1	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
2	7.34 (6.88 to 7.82)	5.58 (5.35 to 5.83)	5.40 (5.18 to 5.63)
3	15.47 (14.62 to 16.36)	10.29 (9.87 to 10.73)	9.89 (9.50 to 10.31)
4	21.55 (20.03 to 23.18)	14.00 (13.22 to 14.82)	13.70 (12.95 to 14.48)
5	19.71 (16.93 to 22.93)	12.98 (11.52 to 14.63)	12.57 (11.18 to 14.14)
6	22.36 (14.58 to 34.30)	16.75 (11.91 to 23.56)	17.17 (12.33 to 23.92)
$CHADS_2$:			
Low risk (0)	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
Intermediate risk (1)	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
High risk (2-6)	12.27 (11.84 to 12.71)	8.30 (8.08 to 8.51)	7.97 (7.77 to 8.17)
CHA_2DS_2-VASc:			
0	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
1	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
2	3.71 (3.36 to 4.09)	3.01 (2.83 to 3.20)	2.92 (2.76 to 3.09)
3	5.92 (5.53 to 6.34)	4.41 (4.21 to 4.61)	4.28 (4.10 to 4.47)
4	9.27 (8.71 to 9.86)	6.69 (6.41 to 6.99)	6.46 (6.20 to 6.74)
5	15.26 (14.35 to 16.24)	10.42 (9.95 to 10.91)	9.97 (9.53 to 10.43)
6	19.74 (18.21 to 21.41)	12.85 (12.07 to 13.69)	12.52 (11.78 to 13.31)
7	21.50 (18.75 to 24.64)	13.92 (12.49 to 15.51)	13.96 (12.57 to 15.51)
8	22.38 (16.29 to 30.76)	14.07 (10.80 to 18.33)	14.10 (10.90 to 18.23)
9	23.64 (10.62 to 52.61)	16.08 (8.04 to 32.15)	15.89 (7.95 to 31.78)
CHA_2DS_2-VASc:			
Low risk (0)	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
Intermediate risk (1)	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
High risk (2-9)	8.82 (8.55 to 9.09)	6.01 (5.88 to 6.14)	5.72 (5.60 to 5.84)

*Includes peripheral artery embolism, ischaemic stroke, and pulmonary embolism.

CHA_2DS_2-VASc was better:

Low risk is lower

Intermediate risk more defined

BMJ 2011; 342:d124

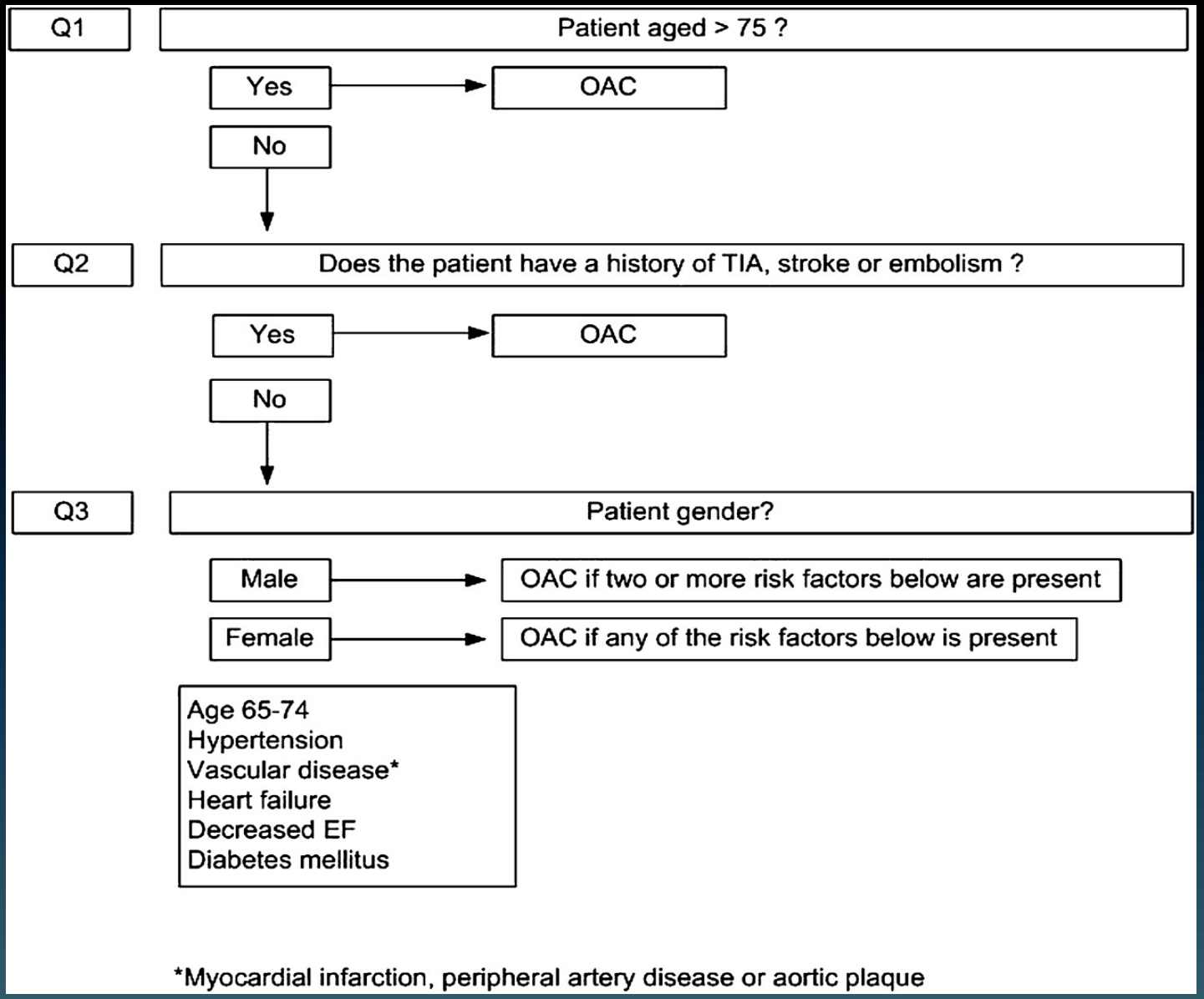
European approach to AF stroke prevention

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75-325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

Take home advantages of CHA2DS2-VASc "Euro-CHADS"

- ***Low risk:*** CHA2DS2-VASc (0) patients at very low risk.
  - No anticoag needed
- ***Intermediate Risk:***
  - With CHADS (1)– 32% patients fall in ASA or Warfarin
  - With CHA2DS2-VASc (1)– only 11% fall in ASA or Warfarin group
- Euro-CHADs has slightly improved c-statistic

Proposed clinical flowchart for stroke prevention in AF



Lip G Y H et al. Chest 2010;137:263-272

Clopidogrel vs VKA: *ACTIVE-W*

THE LANCET

The Lancet, Volume 367, Issue 9526, Pages 1903 - 1912, 10 June 2006
doi:10.1016/S0140-6736(06)68845-4 Cite or Link Using DOI

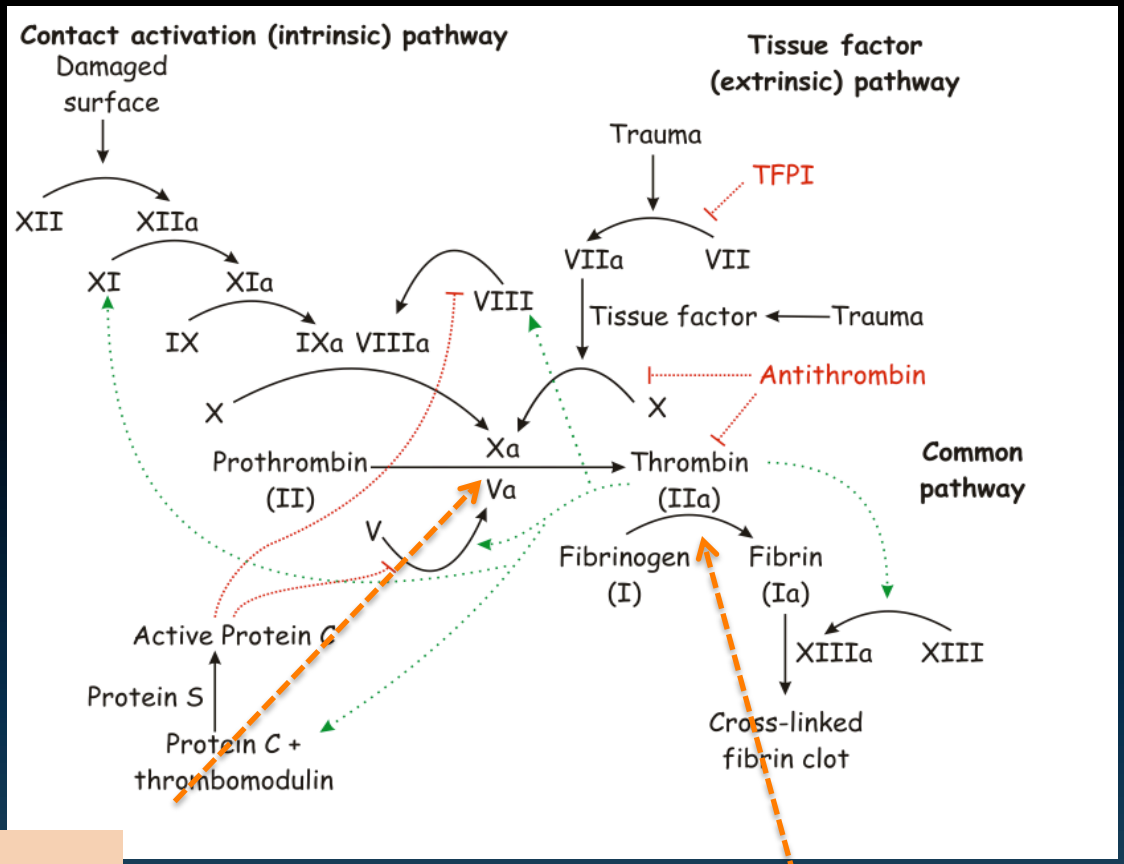
< Previous Article | Next Article

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

The ACTIVE Writing Group on behalf of the ACTIVE Investigators ‡

- Clear superiority of warfarin over clopidogrel (40% Risk reduction)
- Study stopped prematurely due to warfarin benefit

The new oral blood thinners



Factor Xa-Inhibitors

Rivaroxaban

Apixaban

Direct Thrombin Inhibitor

Dabigatran

The then and now…

Dabigatran

- Data
- Clinical caveats
- Limitations

RE-LY Trial

2009

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

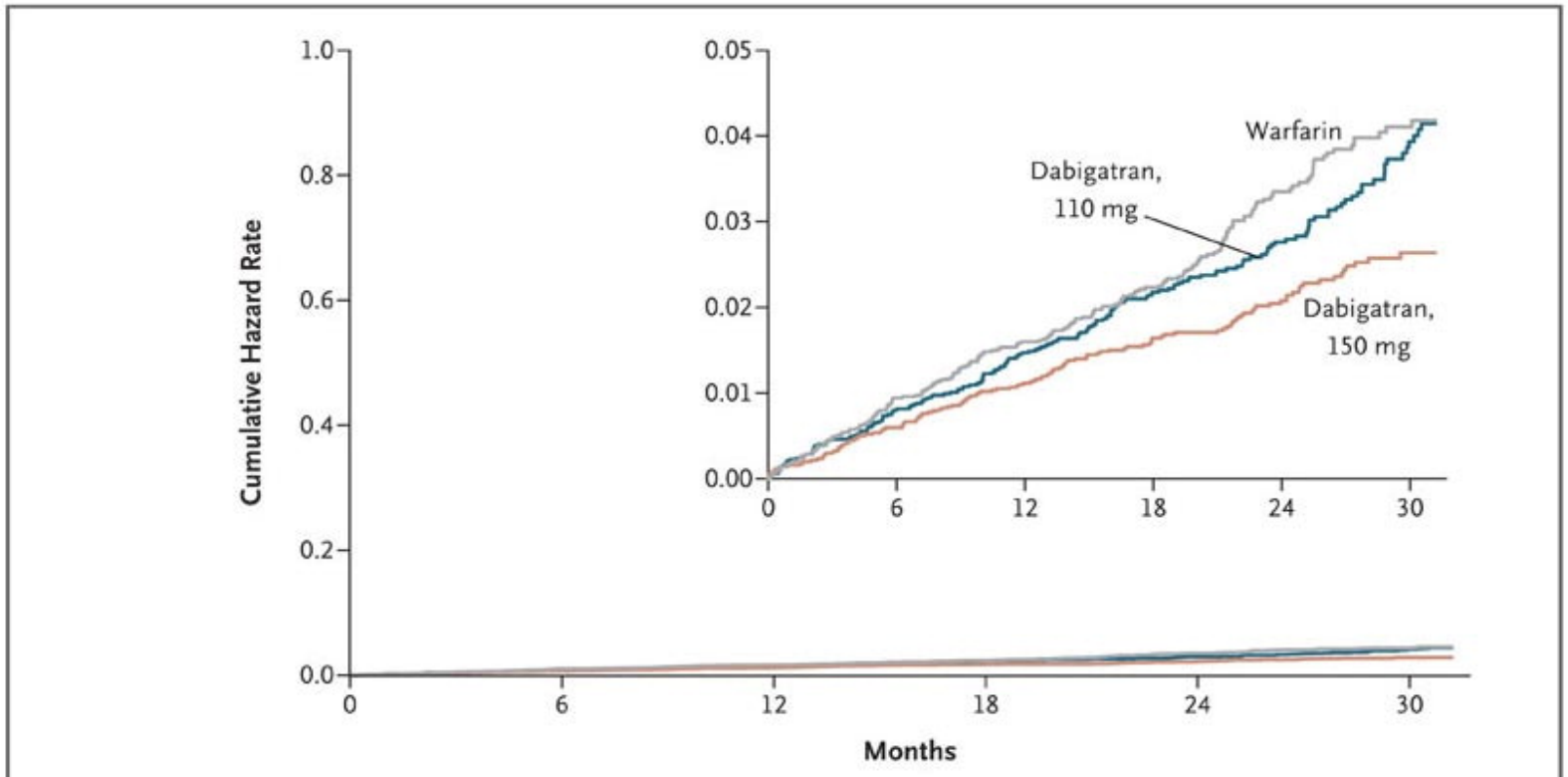
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RE-LY
NEJM 2009

- Methods:
  - 18, 000 AF patients randomized to dabigatran 110mg bid, dabigatran 150mg bid or warfarin
- Results:
  - Average CHADS2 score =2; mean age 71
  - Mean f/u 2 years
  - Warfarin TTR 64%

RE-LY: Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Connolly SJ et al. N Engl J Med 2009;361:1139-1151.

The NEW ENGLAND JOURNAL of MEDICINE

RE-LY: Safety Outcomes

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

RE-LY Bleeding Data

	Warfarin (n= 6022)	Dabigatran 150 (n=6076)	P-Value
Major Bleeds	397	375	p=0.31
Life-threatening bleeds	212	175	p=0.04
ICH	87	36	p < 0.001
GI Bleeds**	129	182	p< 0.001

Dabigatran Facts

- Mechanism of Action
  - Direct Thrombin inhibitor (Final pathway)
- Pharmacology
  - Rapid onset of action (1 hour) and half life 12-14 hours
  - Cleared primarily through kidneys; dose adjustments required when GFR < 30
  - BID dosing
  - No significant drug interactions
  - No dietary interactions
- Adverse Effects
  - 12% reported "dyspepsia."
- Convenience Factors
  - No INR testing

Dabigatran

Positives

- Superior to warfarin
  - Fewer strokes
  - Less ICH
  - Trend toward lower mortality
- No drug interactions
- No dietary interaction
- Convenience
  - No INRs
  - Can be used to acutely anticoagulate: oral "lovenox"

Negatives

- Increased cost
  - May be cost-effective (Annals paper)
- GI Side effects are real
- BID dosing requires compliance
- Trust factor
  - Personal responsibility
- Superiority in low risk patients or those with good INR control is debatable
- Renal adjustments

Dabigatran and Decreased ICH risk:

Is it Dabigatran, or just that warfarin is bad?

Anticoagulation With the Oral Direct Thrombin Inhibitor Dabigatran Does Not Enlarge Hematoma Volume in Experimental Intracerebral Hemorrhage

Arne Lauer, BSc; Flor A. Cianchetti, BSc; Elizabeth M. Van Cott, MD; Frieder Schlunk, BSc; Elena Schulz, BSc; Waltraud Pfeilschifter, MD; Helmuth Steinmetz, MD; Chris B. Schaffer, PhD; Eng H. Lo, PhD; Christian Foerch, MD

Background—The direct thrombin inhibitor dabigatran etexilate (DE) may constitute a future replacement of vitamin K antagonists for long-term anticoagulation. Whereas warfarin pretreatment is associated with greater hematoma expansion after intracerebral hemorrhage (ICH), it remains unclear what effect direct thrombin inhibitors would have. Using different experimental models of ICH, this study compared hematoma volume among DE-treated mice, warfarin-treated mice, and controls.

Methods and Results—CD-1 mice were fed with DE or warfarin. Sham-treated mice served as controls. At the time point of ICH induction, DE mice revealed an increased activated partial thromboplastin time compared with controls (mean±SD 46.1±5.0 versus 18.0±1.5 seconds; $P=0.022$), whereas warfarin pretreatment resulted in a prothrombin time prolongation (51.4±17.9 versus 10.4±0.3 seconds; $P<0.001$). Twenty-four hours after collagenase-induced ICH formation, hematoma volume was 3.8±2.9 μL in controls, 4.8±2.7 μL in DE mice, and 14.5±11.8 μL in warfarin mice (n=16; Welch ANOVA between-group differences $P=0.007$; posthoc analysis with the Dunnett method: DE versus controls, $P=0.899$; warfarin versus controls, $P<0.001$; DE versus warfarin, $P=0.001$). In addition, a model of laser-induced cerebral microhemorrhage was applied, and the distances that red blood cells and blood plasma were pushed into the brain were quantified. Warfarin mice showed enlarged red blood cell and blood plasma diameters compared to controls, but no difference was found between DE mice and controls.

Conclusions—In contrast with warfarin, pretreatment with DE did not increase hematoma volume in 2 different experimental models of ICH. In terms of safety, this observation may represent a potential advantage of anticoagulation with DE over warfarin. (***Circulation*. 2011;124:00-00.**)

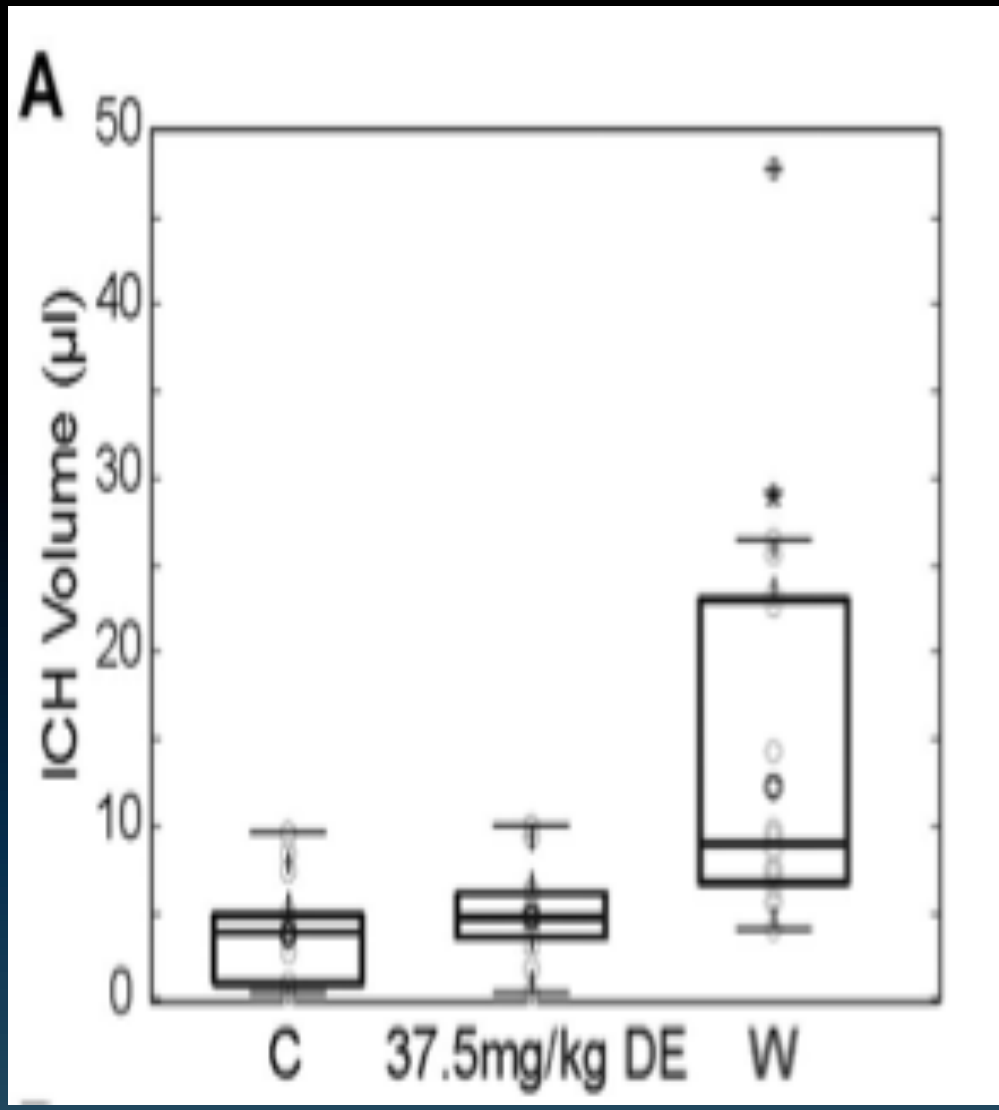
Key Words: anticoagulants ■ cerebral hemorrhage ■ intracerebral hemorrhage ■ warfarin ■ dabigatran ■ stroke

Dabigatran biochemistry

- Compared to warfarin, dabigatran-treated mice fared better with induced ICH

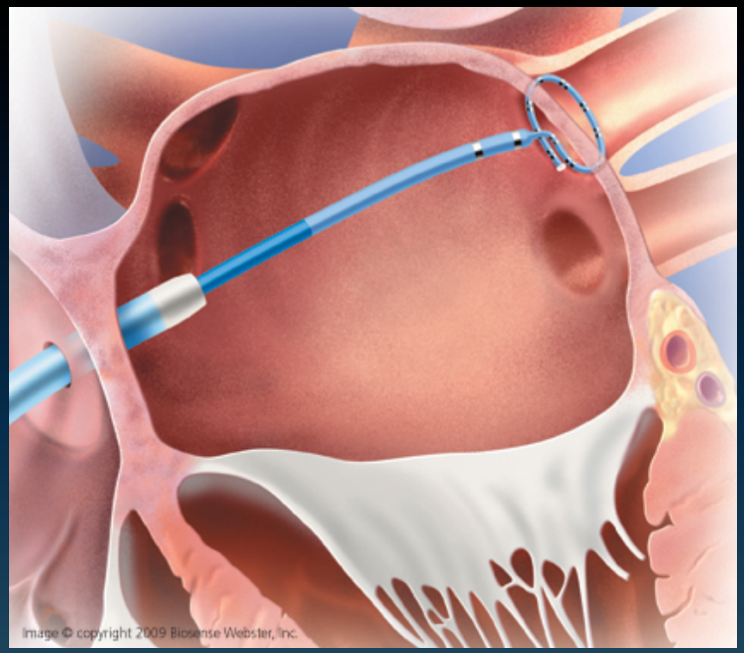
Potential reasons:

- DTI do not inhibit thrombin-activatable fibrinolysis inhibitor generation whereas drugs that target factor Xa (warfarin) do.
  - Dabigatran is a uni-(not bi)valent binder to thrombin. This allows for Dabig-mediated decreases in Factor II activity and sufficient clotting in ICH
- Microhemorrhages induced in warfarin-treated mice more often expand toward having increased RBC and blood plasma diameters whereas microbleeds in DE mice do not differ from controls. Thus, we may speculate that in the RE-LY trial, the absolute number of cerebral micobleeds was similar in the warfarin and the dabigatran groups but that microhemorrhages under warfarin more often expanded to- ward symptomatic ICH.



AF Ablation:

Could AF-ablation Reduce Stroke Rates?



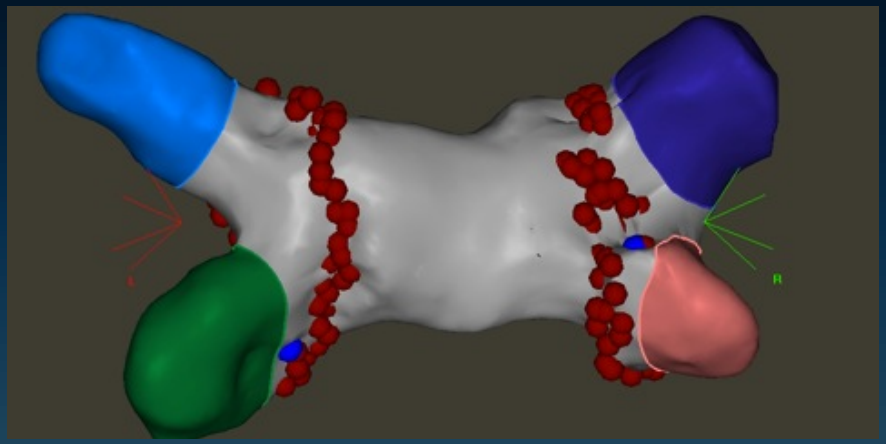


Table 18 Randomized clinical trials of catheter ablation vs. antiarrhythmic drugs or no treatment in AF

Study	Reference	Patients (n)	Age, years	Type of AF	Previous use of AAD	Ablation technique	Repeat ablation in the ablation group	Crossed to ablation in the AAD group	AF free at 1 year	
									Ablation	AAD
Krittayaphong *et al.* 2003	Online	30	55 ± 10 (ablation) 47 ± 15 (AAD)	Paroxysmal, persistent	≥1[a]	PVI + LA lines + CTI ablation + RA lines	Not stated	Not stated	79%	40%
Wazni *et al.* 2005 (RAAFT)	134	70	53 ± 8 (ablation) 54 ± 8 (AAD)	Mainly paroxysmal	No	PVI	12%[b]	49%[c]	87%	37%
Stabile *et al.* 2005 (CACAF)[d]	Online	245	62 ± 9 (ablation) 62 ± 10 (AAD)	Paroxysmal, persistent	≥2	PVI + LA lines ± CTI ablation	No exact data	57%	56%	9%
Oral *et al.* 2006[e]	Online	245	57 ± 9	Persistent	≥1 (mean 2.1 ± 1.2)	CPVA	26% for AF; 6% for LA flutter	77%	74%	4%
Pappone *et al.* 2006 (APAF)	135	198	55 ± 10 (ablation) 57 ± 10 (AAD)	Paroxysmal	≥2 (mean 2 ± 1)	CPVA + CTI ablation	6% for AF; 3% for atrial tachycardia	42%	86%	22%
Jais *et al.* 2008 (A4 study)	133	112	51 ± 11	Paroxysmal	≥1	PVI ± LA lines ± CTI ablation	Mean 1.8 ± 0.8, median 2 per patient	63%	89%	23%
Forleo *et al.* 2008[f]	Online	70	63 ± 9 (ablation) 65 ± 6 (AAD)	Paroxysmal, persistent	≥1	PVI ± LA lines ± CTI ablation	Not stated	Not stated	80%	43%
Wilber *et al.* 2010 (Thermocool)[g]	96	167	55.5 (ablation) 56.1 (AAD)	Paroxysmal	≥1 (mean 1.3)[h]	PVI ± LA lines ± CFAEs ± CTI ablation ± RA lines	12.6% within 80 days after 1st procedure[i]	59%[c]	66%	16%
Packer *et al.* 2010 (STOP-AF)[j]	Online	245	56.7 (ablation) 56.4 (AAD)	Paroxysmal	≥1[b]	Cryo-PVI ± LA lines	19% within 90 days after 1st procedure	79%	69.9%	7.3%

AF ablation

Advantages

- Proven superior to AAD in maintenance of SR
  - Ultimate success rates: 90%
- Proven superior to AAD in QOL
- Safe
  - Two-three hours
  - One –day hospital stay
  - Often off drugs in follow-up
- No data yet on outcomes
  - Stroke?
  - Mortality?

Cons:

- Success often requires two procedures
- Some complications are serious
- Requires general anesthesia
- Though smaller, the procedure is not "Mickey Mouse."
- LA contractility and asymptomatic MRI lesions still a concern
- What about outcomes?

COMPARISON OF LONG TERM STROKE OR TIA RISK BETWEEN PATIENTS WITH ATRIAL FIBRILLATION WHO UNDERGO RADIOFREQUENCY CATHETER ABLATION VS. MATCHED PATIENTS WHO HAVE NOT HAD AN ABLATION PROCEDURE

ACC Poster Contributions
Ernest N. Morial Convention Center, Hall F
Sunday, April 03, 2011, 3:30 p.m.-4:45 p.m.

Session Title: Clinical Electrophysiology --Atrial Fibrillation and Stroke
Abstract Category: 26. Clinical Electrophysiology—Supraventricular Arrhythmias
Session-Poster Board Number: 1056-395

Authors: *Matthew R. Reynolds, Candace Gunnarsson, Tina Hunter, Joseph Ladapo, Jamie March, Sarah A. White, Mingdong Zhang, Steven C. Hao, Beth Israel Deaconess Medical Center, Boston, MA, California Pacific Medical Center, San Francisco, CA*

Background: Evidence informing the role of radiofrequency catheter ablation (RFCA) in the care of patients with AF is growing rapidly, but little is known about long-term outcomes, particularly in regards to the incidence of stroke or TIA. The objective of this study was to compare long term safety for a propensity matched sample of ablation and non-ablation patients with AF.

Methods: We performed a retrospective cohort analysis of the incidence of stroke/TIA in AF patients who underwent RFCA compared to those that were treated with at least two different rhythm-control medications but no ablation. We used a coding algorithm to identify 3,194 RFCA patients and 6,028 non-ablation patients from the Thomson Reuters MarketScan® Research Database. This database contains individual-level claims information from employers, health plans, hospitals, Medicare, and Medicaid. The analytic start date for the RFCA patients was the date of their first ablation and for non RFCA patients it was the date of their second rhythm control medication fill. From this sample, 801 pairs were propensity matched based on 15 characteristics, which included patient demographics, comorbid conditions, medication usage and prior stroke/TIA. The primary outcome measure was a record of stroke or TIA at any time up to 3 years.

Results: Kaplan Meier analysis in the propensity matched pairs demonstrated a significant reduction in stroke/TIA rates for RFCA patients compared to non-ablation patients during the follow-up period. Preliminary findings include a multivariable Cox proportional hazards model, which adjusted for covariates still statistically different after matching (time in the database, baseline diabetes mellitus, rate medication pre time zero), showing a reduction in stroke/TIA rates with RFCA hazard ratio of 0.664 [p=0.04, 95% CI (.45,.98)]. A second multivariable Cox proportional hazards model, which included an additional adjustment of prior stroke/TIA, revealed consistent findings; hazard ratio .695 [p=.07, 95% CI (.47,1.00)].

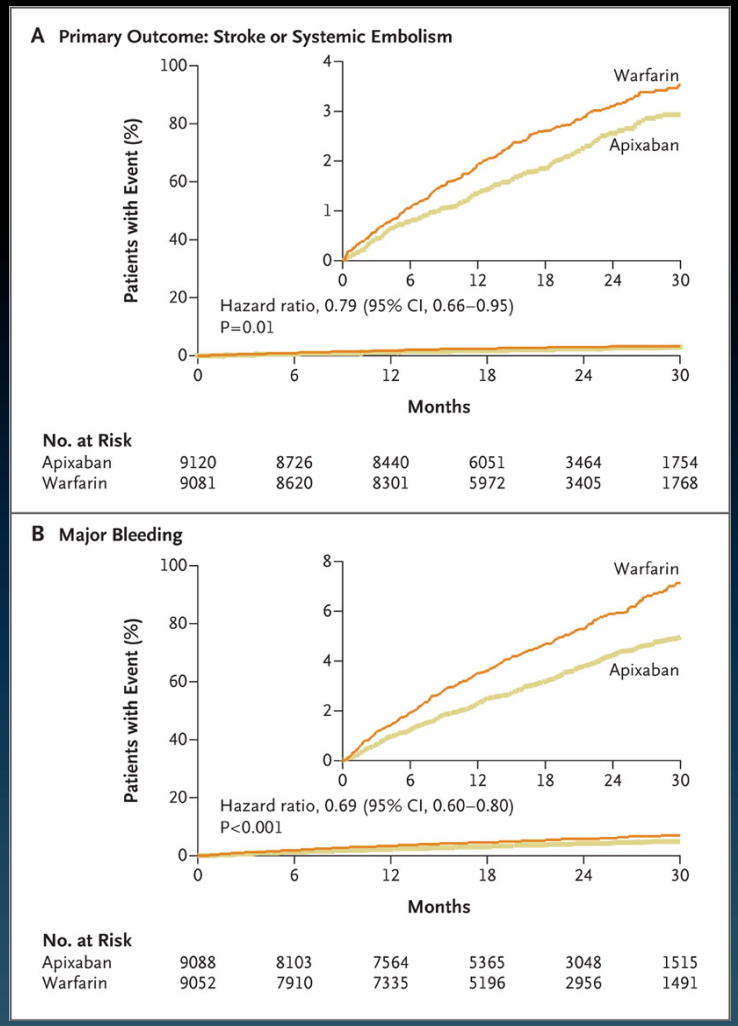
Conclusion: In this analysis, 801 propensity-matched pairs demonstrated a significant reduction in the risk of stroke/TIA in AF patients treated with RFCA.

CABANA Trial

- *CABANA: Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation*
- *RCT looking at Outcomes:*
  - *Stroke*
  - *Mortality*
  - *Efficacy*
  - *QOL*
- *124 Centers*
  - *Enrolled 492; Target 3000*
  - *Enrollment is problem b/c referred patients want cure—not meds*

Most promising in near future…

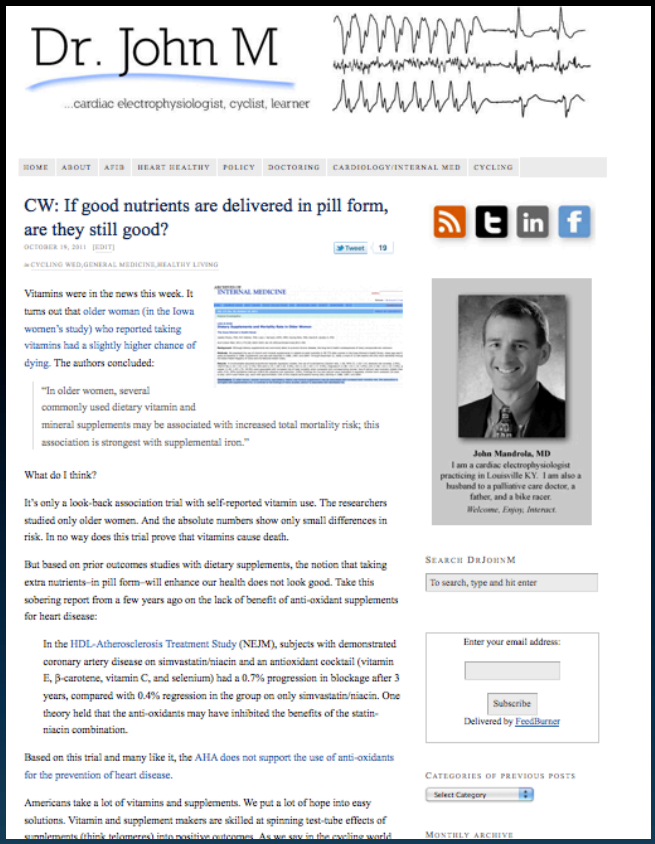
ARISTOTLE Trial: Apixaban



- RCT of 18,000 AF patients
- Apixaban versus warfarin
- Apixaban clearly superior:
  - Marked reduction in stroke
  - fewer bleeds,
  - far-fewer ICH
  - Statistically sig decrease mortality

Apixaban not yet FDA-approved

Thanks…



For more real world information on AF and heart rhythm disorders, visit my blog:
www.drjohnm.org

Granger CB et al. N Engl J Med 2011;365:981-992.

The NEW ENGLAND JOURNAL of MEDICINE

- Where possible, patients at intermediate risk should be considered for oral anticoagulation rather than aspirin, since undertreatment is more harmful than overtreatment.[28,29] Full discussion with the patient with one combination risk factor would enable agreement to use oral anticoagulation instead of aspirin to allow greater protection against ischemic stroke, especially if these patients value stroke prevention much more than the (theoretical) lower risk of hemorrhage with aspirin and the inconvenience of anticoagulation monitoring.[10] As mentioned, the BAFTA trial found no difference in major bleeding between warfarin (INR 2-3) and aspirin 75 mg in an elderly AF population in primary care,[2] and aspirin cannot be regarded as a much safer alternative to VKA.

Topics for Today

- The increasing burden of AF
- New ways to prevent stroke
  - Which AF patients should be anticoagulated?
  - Which drug?
- New recommendations to prevent heart failure
- What is the role of AF ablation?
  - How has the procedure changed?
  - Is the treasure worth the taking the journey?

My tired lines to AF patients…

- *"Welcome to the club. I am sorry. I am a member too."*
- *"You have company: "3 million Americans and more than 5 million Europeans also have AF."*
- *"AF isn't terrible, but it may require us to be friends."*
- *"Worrying about AF is like worrying about getting gray hairs, wrinkles or needing reading glasses."*
- *"AF can be rough, but it isn't life-threatening. We must never make AF treatment worse than AF."*

Is the increasing prevalence of AF related to just age?